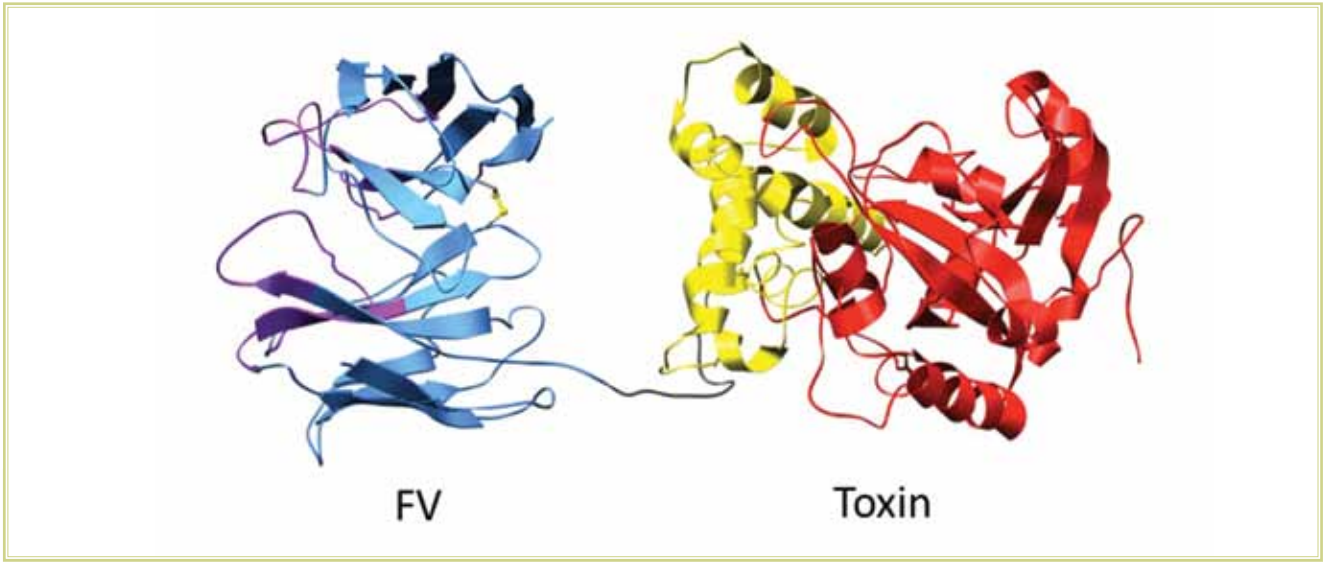
Improving an Immunotoxin

Immunotoxins are chimeric proteins that comprise a targeting domain (e.g., the Fv portion of a monoclonal antibody or ligand) and a toxin domain that is capable of causing cell death.

(Image: I. Pastan, CCR)



The targeting domain includes the Fv portion of monoclonal antibodies specific for antigens preferentially expressed on human cancers.

When targeted specifically to a diseased cell, immunotoxins can be effective treatments for disease. An ideal immunotoxin should be active so that only small amounts need to be given to cause tumor regressions, small in size so that it can penetrate into cancers, stable so it remains functional during the five to ten hours required to reach the interior of a cancer, and low in immunogenicity so it can be given repeatedly. Until recently, this was difficult to achieve due to the inherent immunogenicity of immunotoxins when administered to humans.

Ira Pastan, M.D., Co-Chief of CCR's Laboratory of Molecular Biology, has designed and produced recombinant immunotoxins with these desirable properties through his work on *Pseudomonas* exotoxin A (PE). PE was first improved by removing portions of the toxin that were not required for its cell-killing activity. This modification decreased the size of the molecule while also removing undesirable protease sites, resulting in a more stable molecule. PE was further improved by reducing its immunogenicity by identifying and removing B cell and T cell epitopes, through deletion and point mutation of key amino acids. These modifications allow the repeated administration of a PE that retains its cell-killing activity.

The modified PE has been attached to several targeting domains, and the resulting immunotoxins are being investigated in clinical trials. The targeting domains used so far include the Fv portion of monoclonal antibodies to antigens that are preferentially expressed on human cancers, such as mesothelioma and ovarian and pancreatic cancer (anti-mesothelin antibodies), and several types of B cell leukemias (anti-CD22 antibodies). These improved immunotoxins are very promising prospects as treatments for patients suffering from cancer. Notably, the toxin can be attached to any targeting domain for use as a treatment of a number of different diseases.

The NIH currently is pursuing patent rights that cover these immunotoxins. Many of them are available for licensing. For more information, please contact Dave Lambertson, Ph.D., (lambertsond@mail.nih.gov) in the NIH Office of Technology Transfer.